TRANSLATION

(11) Patent Specificition DD 297 062 A5

(12) Exclusive Patent
(19) Federal Republic of Germany
Granted in accordance with § 17, Article 1, of the Patent Code of the DDR [German Democratic Republic] of October 27, 1983
in accordance with the corresponding regulations in the Treaty of Unification
5(51) A 61 K 33/06

GERMAN PATENT OFFICE Published in the version submitted by Applicant
(21) DD A 61 K / 343 612 3
(22) August 23, 1990
(44) January 2, 1992
(71) see (73)
(72) Prof. Dr. sc. med. Wolfgang DIEZEL, Germany
(73) TKS Optimum GmbH of Wartenberger Straße 24, O-1092 Berlin, GERMANY

(54) Process for Preparing a Novel Topical Dermatic [Drug for Skin Treatment] with Anti-inflammatory Action

(55) A topical dermatic; anti-inflammatory action; magnesium ions; magnesium salts, lanthanum ions, lanthanum salts; therapeutic application, non-toxic; medicine; pharmaceutical industry; cosmetics industry.

(57) The invention relates to a process for preparing a novel topical dermatic [drug for skin treatment] with anti-inflammatory action. After topical application, magnesium ions or magnesium salts and lanthanum ions or lanthanum salts can influence inflammatory skin diseases (eczema, psoriasis, etc.) in a therapeutically effective way or cure the same. Being non-toxic, magnesium ions are particularly suitable for therapeutic application in the case of humans. The anti-inflammatory effect of the ions can be enhanced by ultra-violet light. Medicine, the pharmaceutical industry, and the cosmetics industry are the fields of application of the invention.

ISSN 0433-6461

5 pages

IRN 413151 EP01

Claims:

1. A process for preparing medications which are suitable for the therapy of inflammatory skin diseases or reduce allergic inflammatory reactions, characterised in that magnesium ions are used alone or in combination with lanthanum ions.

2. The process according to Claim 1, characterised in that magnesium salts in concentrations of 1.0 to 28.0 % by weight alone or together with lanthanum ions (0.1 to 0.5 % by weight) are blended into ointment bases, lotions, solutions, toothpastes, and cosmetics.

3. The process according to Claim 1 and 2, characterised in that magnesium ions (1.0 to 28.0 % by weight) alone or together with lanthanum ions (0.1 to 5.0 % by weight) are blended into ointments or creams and are therapeutically used in combination with ultraviolet light.

4. The process according to Claim 1 nd 2, characterised in that magnesium ions (1.0 to 28.0 % by weight) alone or together with lanthanum ions (0.1 to 5.0 % by weight) are dissolved in water and therapeutically used in combination with ultraviolet light (balneo-photo-therapy).

5. The use of magnesium ions or lanthanum ions according to Claims 1 to 3 for preparing topical dermatics, improved medicinal waters, novel toothpastes, and cosmetics.

Field of application of the invention

The invention relates to a process for preparing medications which are suitable for the therapy of skin diseases of inflammatory origin (eczema and psoriasis, etc.). Medicine, the pharmaceutical industry, and the cosmetics industry are the fields of application of the invention.

Characteristics of the known state of the art

Inflammations of the skin develop when inflammation mediators are generated by "inflammation enzymes". The following inflammation mediators are formed by the enzymes phospholipase A2 and the lipoxygenases: leucotrien B4, C4, D4 and 5-hydroxytetraeicosanic acid (J. Chang et al., Biochem. Pharmacol. **36** [1987] 2429 - 2436; S. Forster et al., Br. J. Dermatol., **112** [1985], 135 - 147; B.A. Burall et al., J. Invest. Dermatol., **91** [1988], 294 - 297; N.A. Sater et al., J. Invest. Dermatol., **80** [1983], 115 119; P.M. Downd et al., J. Invest. Dermatol., **84** [1985], 537 - 541).

The inflammation mediators act in chemotactical fashion on "inflammation cells" (primarily on neutrophilic granulocytes), whereby any inflammation is enhanced and maintained. To date inflammations of the skin were treated preferably with glucocorticoids. Glucocorticoids are therapeutically effective because they inhibit the inflammation enzyme phospholipase A2 so that no inflammation mediators develop (K.H. Kaldberg et al., Arch. Dermatol., **112** [1976], 800 - 810). Disadvantages result from the topical application of glucocorticoids (review: W. Siegenthaler et al., Klinische Physiologie, Georg-Thieme Publishers, Stuttgart, New York, 1982, p. 397):

- Skin atrophy and premature aging of the skin develop upon frequent topical application.
- In large-area therapeutic applications, glucocorticoids are absorbed and metabolic disorders may result (increase in the blood sugar level or triggering diabetes mellitus).

Goal of the invention

The goal of the invention is to provide the medical practice with novel medications which can be used for the therapy of inflammatory skin diseases (eczema, psoriasis). It is the guiding principle to inhibit competitively inflammation enzymes of the skin by magnesium ions (but also by lanthanum ions in combination with magnesium ions). As a result of this inhibition, inflammation mediators do not develop - any inflammation of the skin is inhibited or cannot be triggered.

Description of the essence of the invention

The goal underlying the invention is to develop a process and medications which are suitable for the preparation of topical dermatological medications or which inhibit skin inflammations. The problem is solved by incorporating magnesium ions or magnesium ions together with lanthanum ions into ointment bases or by dissolving magnesium salts in water (or other liquids).

The phlogogenic enzymes of the skin (the phospholipase A2 or the lipoxygenases) require calcium ions as co-enzyme to be fully functional (S. Forster et al., Br. J. Dermatol., **112** [1985], 135 - 147; B.A. Burrall et al., J. Invest. Dermatol., **91** [1988], 294 - 297; T. Hofmann et al., J. Immunol. **140** [1988] 3912 - 3918). Calcium ions and magnesium ions or lanthanum ions have similar dimensions of the molecules and can bind to similar protein structures. But the affinity of binding of the calcium ions is higher. In the case of high magnesium concentrations, the calcium ions are expelled from their specific binding sites (E. Carafoli, Ann. Rev. Biochem., **56** [1987]. 395 - 443). Enzymes which require calcium ions as co-enzyme (the phospholipase A2 as the limiting enzyme for the release of arachidonic

acid and also the epidermatic lipoxygenases) are therefore competetively inhibited by high magnesium concentrations. The inhibition of inflammatory processes is the consequence. Magnesium ions are particularly suitable for the inhibition of the phlogogenic enzymes and, hence, for the suppression of inflammatory processes because they are non-toxic in topical applications (R. Ludewig and K. Lohs: Akute Vergiftungen [Acute Poisoning], Gustav-Fischer Publishers, Jena, 1982, pp. 297 - 298).

Examples of embodiments

Example 1: Excessive contact sensitivity to contact with 1-chloro-2,4-dinitrobenzene (DNCB) - detection and inhibition by $MgCl_2$.

BALB/c mice (5 animals per group) were sensitised to DNCB as follows: application of 25 µL of a 1% DNCB solution (DNCB, dissolved in acetone-olive oil, 4:1) on three successive days (days -3, -2, -1) on a skin area on the back (0.5 x 0.5 cm) after previous shaving. After five days (day +5), 25 µL of a 0.5 %, 0.25 % or 0.125 % DNCB solution without or with various $MgCl_2$ concentrations (Table 1) were applied onto the dorsal surface of the two ears of the same animals (measured pre-DNCB-data). The solution containing DNCB and $MgCl_2$ was prepared as follows: $MgCl_2$ was dissolved in 95 % ethanol:glycerin (4:1); DNCB, in 4:1 acetone-olive oil. After that, the two solutions with the concentrations listed in Table 1 were mixed. DNCB alone was applied in the mixture ethanol:glycerin:acetone:olive oil. Twenty four hours later (day +6), the thickness of the ear (measured post-DNCB data) was measured with a micrometer (of the company Peacock Inc., Tokyo). The increase in ear thickness is a consequence of the contact sensitisation to DNCB after the primary 3-day DNCB application (day -3, -2, -1). It is obtained as the difference between the measured post-DNCB data and the measured pre-DNCB data. It is recognised (Table 1) that $MgCl_2$ importantly blocks the inflammatory effect triggered by DNCB. By contrast, NaCl does not have a similar effect (Table 1, comparison No. 7 with no. 8; $p < 0.01$).

Table 1
DNCB sensitisation and inhibition of contact dermatitis by magnesium ions (BALB/c mice)

group of animals[1]	"challenge"	substance	increase in ear thickness [2] (mm ± SE)
1	DNCB	0.5 %	0.16 ± 0.02
2	DNCB + $MgCl_2$	0.5 % 28. %	0. + 0.03
3	DNCB	0.25 %	0.14 ± 0.02
4	DNCB + $MgCl_2$	0.25 % 28. %	0.10 + 0.02
5	DNCB	0.125 %	0.14 ± 0.02
6	DNCB + $MgCl_2$	0.125 % 28. %	0.02 + 0.01
7	DNCB + $MgCl_2$	0.125 % 14. %	0.06 + 0.02
8	DNCB + NaCl	0.125 % 14. %	0.11 + 0.02
9	control (DNCB 0.25 %, no primary DNCB sensitisation)		0.02 + 0.01

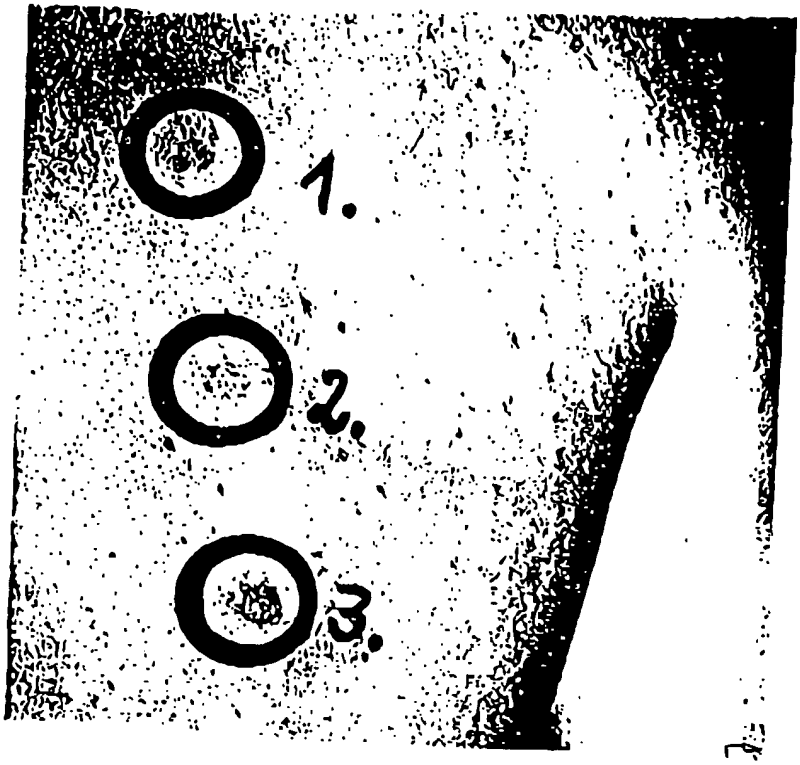
1 Each group of animals comprises 5 male BALB/c mice, age between 4 and 6 weeks
2 Measured post-DNCB data minus measured pre-DNCB data.
Statistical differences (WILCOX ON text): No. 1/2, no significant difference; No. 3/4: no significant difference; No. 5/6: $p < 0.001$; No. 5/7: $p < 0.01$; No. 7/8: $p < 0.01$.

Example 2: Epicutaneous application of formaldehyde in combination with, or without, $MgCl_2$ on patients with formaldehyde allergy

The epicutaneous application of $MgCl_2$ together with formaldehyde (patients with formaldehyde allergy) renders a reduced inflammatory reaction in dependence upon the magnesium chloride concentration (Figure 1). In order to detect the inflammation-inhibiting action of $MgCl_2$, $MgCl_2$ in final concentrations of 28 % or 14 % was incorporated into the ointment base unguentum emulsificans aquosum. Composition of the ointment base: alcoholes emulsificantes nonionogeni [non-ionogenic emulsifying alcohols] 21.0%, cera perliquida [liquid wax] 10 %, glycerolum [glycerin] 5 %, propylhydroxybenzoicum 0.06 %, methylhydroxybenzoicum 0.14 %, ethanolum (90 % by volume) 1.8 %, aqua bidestillata [double-distilled water] 62.0 %. Formaldehyde of 5 % was blended into the ointment base. A similarly reduced inflammatory effect due to magnesium ions was also observed on patients having nickel allergy or chromate allergy. Also lanthanum ions in a concentration from 0.5 % to 5 % had a similar concentration-dependent anti-inflammatory effect (Figure 2).

Figure 1

Application of formaldehyde in combination with, or without, $MgCl_2$ on a patient with formaldehyde allergy



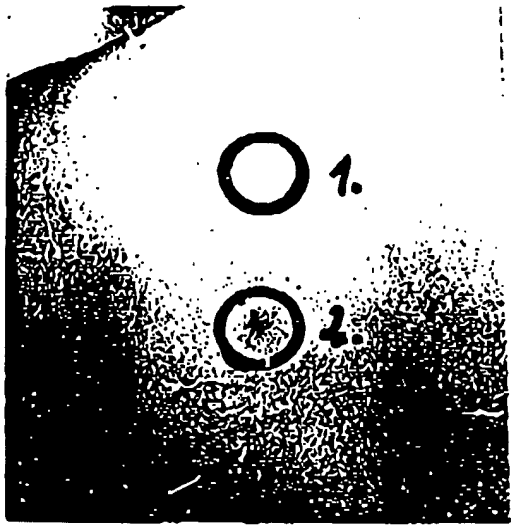
Composition: (1)	formaldehyde	5.0
	$MgCl_2$	28.0
	unguentum emulsificans aquosum to	100.0
Composition: (2)	formaldehyde	5.0
	$MgCl_2$	14.0
	unguentum emulsificans aquosum to	100.0
Composition: (3)	formaldehyde	5.0
	unguentum emulsificans aquosum to	100.0

Absolute amounts applied to a skin area of 0.5 cm x 0.5 cm: 0.45 mg formaldehyde; $MgCl_2 \times 6H_2O$ (28 %): 2.52 mg = 1.38 mol/L; $MgCl_2 \times 6H_2O$ (14 %): 1.26 mg = 0.69 mol/L

The photos were made 24 hours after application of the test substances.

Figure 2

Application of formaldehyde in combination with, or without, $LaCl_3$ on a patient with formaldehyde allergy



Composition: (1)	formaldehyde	5.0
	$LaCl_3$	5.0
	unguentum emulsificans aquosum to	100.0
Composition: (2)	formaldehyde	5.0
	unguentum emulsificans aquosum to	100.0

The photos were made 24 hours after application of the test substances.

Example 3: Preparation of inflammation-inhibiting dermatological medications for topical application

It is proposed in accordance with the invention to blend magnesium ions or magnsium ions together with lanthanum ions into water-containing ointment bases, lotions, toothpastes or waters. Magnesium ions or magnesium salts are particularly suitable as inflammation-inhibiting skin medications because they are non-toxic for humans.

Composition:	$MgCl_2$ [1]	28.0 [2]
	unguentum emulsificans aquosum to	100.0
	[2] concentration ranges:	1.0 to 28.0 % by weight
Composition:	$MgCl_2$	14.0 [1]
	unguentum alcohol. lanae aquosum to	100.0
	[2] concentration ranges:	1.0 to 14.0 % by weight
Composition:	$MgCl_2$	28.0 [1]
	water to	100.0

[1] $LaCl_3$ in concentrations of 0.1 % to 5.0 % can be blended in place of $MgCl_2$ into the ointment base or $MgCl_2$ together with $LaCl_3$ in the above-indicated percentages by weight can be blended into the ointments or dissolved in water (salt concentration identical with that of the Dead Sea).

[2] Concentration ranges: 1.0 to 28.0 % by weight.